is it suggested that the polymersome is proteinaceous. Support is also found at least at page 16 that the polymersomes of the present invention "self-assemble." Accordingly, there is no need for further "post-assembly polymerazation or crosslinking."

Examiner Kishore is thanked for his efforts to work with Applicants to resolve the outstanding issues in this matter. It is truly unfortunate that the Office has been unable to locate the prosecution history for Applicants' application since our conversations began with Examiner Kishore almost a month ago. Nevertheless, rather than incur additional extensions of time Applicants file this response with the accompanying Request for Continued Examination with the understanding that further changes may be proposed to the claims or arguments presented as a result of discussions with the Examiner while the Request for Continued Examination is being processed.

Regarding the Rejections under 35 USC §112/§101:

The Examiner has maintained the rejection of claims 15–16, 21, 23 and 27–29 as indefinite for failing to cite steps involved in the claims method/process: However, Applicants are at a loss to understand this rejection.

Applicants claim a method of using the disclosed polymersomes. They do not claim, in the cited claims, a method for preparing a polymersome. Accordingly, claims 15 and 26, upon which the remaining cited claims depend, are each written as a series of steps. Claim 15 comprises:

> preparing the polymersome vesicle;
> importing into the polymersome at least one encapsulatable material from the environment immediately surrounding the polymersome; and
> transporting the polymersome and the at least one material encapsulated therein away from the surrounding environment, thereby removing it from said environment.

Claim 26 comprises:

> preparing the polymersome vesicle;
> encapsulating therein at least one encapsulatable material;
> delivering the polymersome comprising the at least one encapsulated material to a selected environment; and
> releasing said encapsulated material(s) into the environment immediately surrounding the polymersome.

Why these steps are not acceptable to the Office will be discussed further with the Examiner. However, Applicants respectfully submit that for the reasons of record, Applicants claims are neither indefinite, nor do they lack utility.

Moreover, the Examiner has maintained the argument that the claims are indefinite because the polymersomes may be used to either deliver materials, such as a drug or a dye, into an environment, such as a patient, or they may be used to remove a spent material from a patient. The same polymersome would not be acting to serve both functions simultaneously. The properties of the polymersome would dictate its preferred use. Some are delivery vehicles. Some are used to absorb materials from a particular environment to remove the material from that environment.

However, why this principle is unclear to the Examiner is not understood by Applicants. If the Examiner wishes to restrict Applicants to one function or the other in this particular application, that would be understood. But Applicants' representative is awaiting discussions with the Examiner to further understand the rejection, as well as the problem with the list of possible materials that may be carried by the polymersome. Meanwhile, Applicants rely upon the reasons of record for responding to this rejection.

Applicants respectfully submit that, in fact, the rejections have been overcome and all claims are in condition for allowance.

Regarding the Rejections under 35 USC §102(b)/§103:

The Examiner has maintained the rejections under §102(b) and §103. Because the same references (Ding 1998; Cornelissen 1998; Fendler 1984) have been cited in each, Applicants respond to both rejections together.

The independent claims upon which all others depend have been amended. By specifying that the aqueous solution has been prepared "without the use of organic solvent" overcomes the teachings of Ding *et al.*

Ding *et al.* did not make it obvious to one of ordinary skill in the art that our claimed diblock copolymer super-amphiphile would assemble into vesicles "without the need of organic solvent" and "without post-assembly stabilization by crosslinking." Accordingly, as amended, the present claims are clearly distinguished from the prior art of Ding *et al.* in at least four ways.

Ding *et al.* teaches assembly of vesicles from a diblock copolymer that has a block-selective solubility in *two different organic solvents* rather than a single aqueous solvent.. Neither of Ding *et al*'s polymer blocks favors aqueous solution as a hydrophilic polymer does by definition. Since amphiphilic copolymers require at least one block to be hydrophilic, Ding *et al.* does not teach vesicle formation from super-amphiphilic copolymers.

Ding *et al.* teaches assembly of vesicles in THF and hexane mixtures, i.e. in highly toxic ORGANIC SOLVENTS. Statement "More hexane was added just before irradiation because it was supposed to increase the rigidity of the PCEMA shell (due to reduced PCEMA swelling by THF)" (see Vesicle Preparation on page 6108) suggests that the core of the vesicles, PCEMA, retains fraction of the organic solvent (THF) after the vesicle assembly. Complete removal of organic solvents after assembly is in general very difficult to achieve (in part due to the excellent solubility of the block in that particular solvent).

Ding *et al.* further teaches preparation of vesicles that requires post-assembly crosslinking for stability in water and therefore the final product is covalently bonded. There is a major difference between vesicles that do not require post-assembly polymerization or crosslinking and vesicles that have been crosslinked: (1) they have significantly different material properties, for example the non-cross-linked vesicles are fluid whereas the cross-linked vesicles are solid; (2) they have significantly different chemical properties, for example the non-cross-linked vesicles remain an assembly of large number of molecules whereas the cross-linked vesicles can be in principle only one molecule (or the number of molecules that comprises the vesicle is significantly reduced).

The present invention is also different from Ding *et al* in that the reference teaches preparation of vesicles that can be dispersed only in water, but which precipitate in the presence of NaCl (*i.e.*, are unstable under physiological conditions): "When first prepared in water containing NaCl salt, the PHI-*b*-PCEMA hollow nanospheres precipitated readily" (see Properties of the PHI-b-PCEMA Hollow Nanospheres , page 6111). Moreover, Ding *et al.* could not establish "the degree of isoprene double bond conversion" (Hydroxylation of the PI Chains, page 6110), and therefore the vesicles

taught by the refence can also aggregate due to the "intervesicle linking through the PI chains" (see Properties of the Hairy Hollow Nanospheres, page 6110).

Ding *et al.* thus teaches assembly in organic solvents, stabilization by crosslinking in organic solvents, transfer from organic solvents to water, and subsequent chemical conversion of the hydrophobic blocks into hydrophilic blocks. Moreover, Ding *et al.* does not utilize amphiphilic diblock copolymer at all; and thereby it cannot teach vesicle formation from super-amphiphiles as claimed in the present invention. In sum, Ding *et al.* teaches only crosslinked vesicles, and therefore Ding's vesicles are different and do not meat the requirements of the Applicants' instant claims. Furthermore, Ding *et al.*, alone or combined, does not teach vesicle formation from super-amphiphiles, and therefore the assembly is not driven by the amphiphilic nature of the copolymer. Accordingly, the present invention is neither anticipated by, nor obvious in light of Ding.

Regarding the teachings of Cornellisen *et al.*, the reference fails to show to one of ordinary skill in the art that the "wholly synthetic and non-peptide" diblock copolymer super-amphiphile of the present invention would assemble into vesicles. The claims as amended are distinguished from Cornelissen *et al.* in at least three ways.

$PIAA_{10}$ denotes a polymer containing peptides of L-alanine amino acids, which occur in a vast majority of proteins in nature. Hydrogen bonding between peptides in Cornelissen *et al.* drives helix formation within each polymer ("helical superstructures" – see title of the publication), leading to a structure that they "compare with natural systems, for example, with helix bundle proteins, which contain alpha helices" (last paragraph on page 1429). The chiral character of L-alanine and the helical superstructure intrinsic to $PIAA_{10}$ are described in Cornelissen *et al.* as crucial for the "packing of helices" in the various self-assemblies (last paragraph on page 1429). Specifically, Cornelissen *et al.* teaches self-assembly of peptide-containing molecules based on "chirality" (see first sentence of the publication) and an "attractive interaction between the rodlike headgroups" (last paragraph on page 1428) with "formation of intermolecular hydrogen bonds" (also last paragraph on page 1428).

In contrast to Cornelissen *et al.*, Applicants have used *wholly synthetic,* and not peptide based diblock copolymers. In other words, the present polymersomes do not consist of any naturally occurring repeat units (such as the dipeptide), whose assembly

does not require folding of the polymer into helical rods (or any other stable conformation); whose assembly does not require chirality; whose assembly does not involve intermolecular electrostatic interactions; and whose assembly does not require intermolecular hydrogen bonding.

There are major differences between our claims and the prior art of Cornelissen *et al.* and therefore Cornelissen's vesicles cannot meet the requirements of the amended instant claims. Some of the important differences between our claims and the prior art of Cornelissen *et al.* include:

- The absence of amino acids and peptides in a wholly synthetic and not peptide based block copolymer has at least two important implications: It eliminates the possibility of being degraded by proteases either in organisms or in any environment. Thus the wholly synthetic polymers should prove to be more stable.
- Naturally occurring proteases do not distinguish between natural amino acids made by nature and chemically synthesized natural amino acids. Therefore, a clear distinction must be made between copolymers that have been made completely by chemical synthesis but still consist of naturally occurring repeating units and wholly synthetic copolymers that are not based on naturally occurring repeating units.
- A wholly synthetic and non-peptide –based diblock copolymer significantly reduces the immunogenic potential in a patient or animal, for at least three reasons:
    - due to the absence of natural amino acids and peptides which are generally known to be antigenic;
    - due to the fact that the diblock copolymer does not fold into any naturally occurring rigid structure, since the rigidity of the components or assembly provide stable target for antibody formation or subsequent binding; and
    - due to the fact that the diblock copolymer is not chiral, since chirality is also a structural property that is likely to facilitate antibody formation.

Since the assembly of Applicants' claimed polymersomes does not involve intermolecular electrostatic interactions, their formation can be done under a significantly broadened range of conditions (especially physiological conditions). The claimed vesicles form independently of pH (whereas Cornelissen *et al.* specifically teach vesicle formation in pH = 5.6 where the electrostatic interactions are optimized; near physiological conditions of pH = 7. No assembly occurs for a related $PIAA_{20}$ copolymer, although no vesicles were specifically disclosed for near the $PIAA_{10}$ polymer). Moreover, the claimed vesicles form independently of the presence of any counter ions.

In sum, Cornelissen *et al.* uses naturally occurring repeating units (dipeptide) and therefore the vescles of Cornelissen *et al.* are different from, and do not meet the requirements of Applicants' instant claims. Consequently, Applicants' invention is neither anticipated by nor rendered obvious by Cornelissen *et al.*, who clearly state the importance of peptide-based structure and interactions beyond amphiphilicity for self-assembly. In other words, Cornelissen *et al.* do not teach vesicle formation from super-amphiphiles that depends strictly on the amphiphilic nature of the copolymer, nor would it be obvious from the cited prior art, alone or combined, that super-amphiphiles could form vesicles without further electrostatic or hydrogen-bonding interactions.

Regarding, the teachings of Fendler *et al.*, it would not be known to one of ordinary skill in the art that Applicants' claimed diblock copolymer super-amphiphile would assemble into vesicles "without post-assembly stabilization by crosslinking." As amended, Applicants' claims distinguish from the prior art of Fendler *et al.* in at least two ways.

Fendler *et al.* teaches vesicle assembly only from polymerizable lipids which are not super-amphiphilic molecules that are polymeric, having a number average molecular weight ≥1400. As a result, the vesicles taught by Fendler *et al.* do not possess any advantage over the previously used lipid vesicles unless they are polymerized or crosslinked after assembly.

Fendler *et al.* teaches vesicle stabilization by crosslinking, tpo which Applicants' present claims make no reference since post-assembly crosslinking or polymerization of the membrane assembly can be omitted altogether and unnecessary.

In sum, Fendler *et al.* teaches crosslinked vesicles and therefore the vesicles in the cited reference are different and fail to meet the elements of Applicants' instant claims. Furthermore, Fendler *et al.* does not teach vesicle formation from super-amphiphiles, rather they are from

modified natural lipids. Accordingly, Applicants' invention would be neither anticipated by nor rendered obvious by Fendler *et al.*, since there is no suggestion, alone or combined, that super-amphiphiles could form vesicles in aqueous solutions.

Therefore, in sum, Applicants respectfully submit that all arguments regarding anticipation or obviousness have been overcome in Applicants' present claims. Expert Declarations are available stating the foregoing facts, and will be submitted if requested by the Examiner to assist in making a decision. Vesicles that are assembled or stabilized by other means than amphiphilicity have major limitations (different stability, narrow range of solubility, fluidity, to name just few). Their material and chemical properties are dramatically different and they do not meet the requirement of the current instant claim. The assembly of any super-amphiphiles into vesicles in aqueous solutions (without organic solvents) has never been achieved based on the strictly amphiphilic character of the molecules in any prior art, and therefore it cannot be considered obvious. Accordingly, it is respectfully submitted that all pending claims are in condition for allowance, and respectfully request that allowance be granted at the earliest date possible. Should the Examiner have any questions or comments regarding Applicant's amendments or response, the Examiner is asked to contact Applicant's undersigned representative at (215) 575-7034.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0979.

Respectfully submitted,

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